Spaceflight-induced Bone Loss: Countermeasures & their Evaluations

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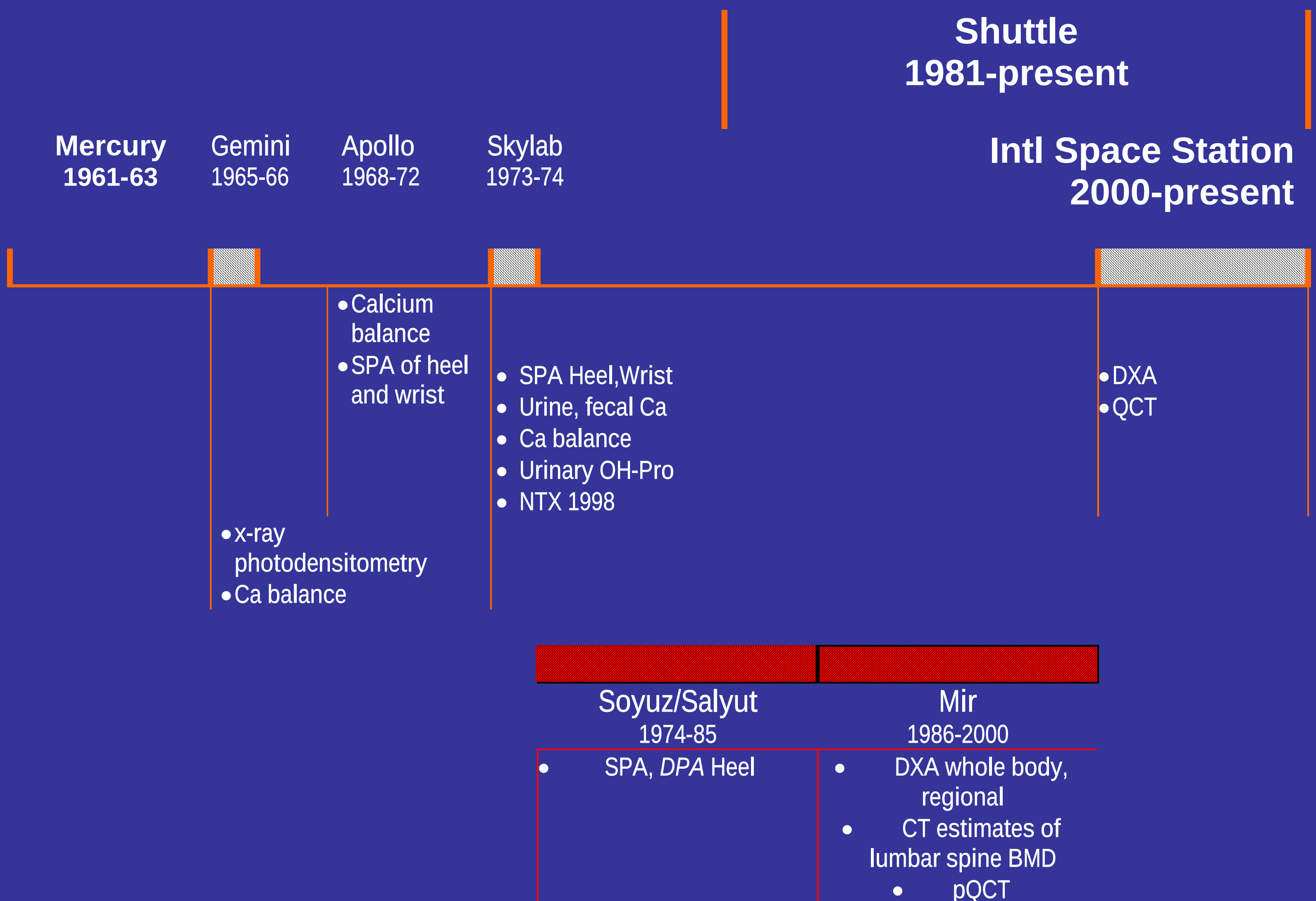
Learning Objectives

- Understand the biomedical effects of spaceflight and their associated health risks.
- Understand how the “Factor of Risk” for fracture can be calculated in the adult skeleton for space travel
- Understand how various countermeasures [CMs] influence the Factor of Risk.

Overview

- Review: Spaceflight changes in BMD
- Ground-based models
- Countermeasures for bone loss
- Flight Analog project at JSC/UTMB

Early Missions: Skeletal Measurements



BMD loss is site-specific and rapid.

Index DXA aBMD g/cm2	**%/Month Change ± SD**
Lumbar Spine	-1.06±0.63*
Femoral Neck	-1.15±0.84*
Trochanter	-1.56±0.99*
Total Body	-0.35±0.25*
Pelvis	-1.35±0.54*
Arm	-0.04±0.88
Leg	-0.34±0.33*
*p<0.01, n=16-18	**LeBlanc et al, 2000**

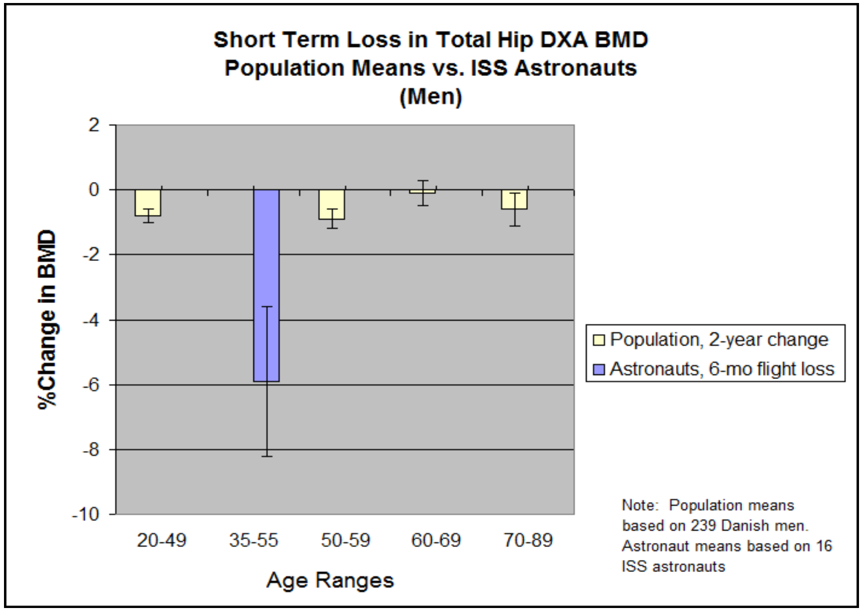
NASA-Mir

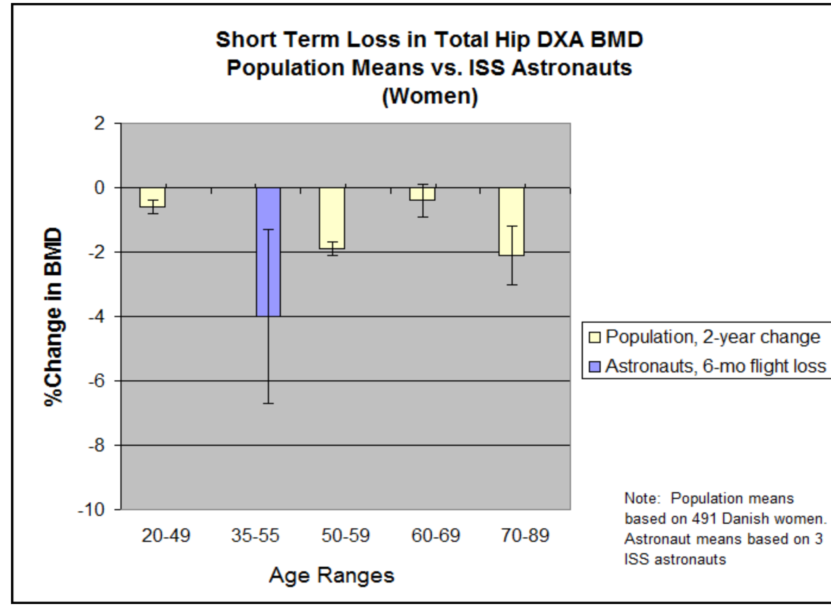
Total Bone Loss after 4-6 month Spaceflight Missions

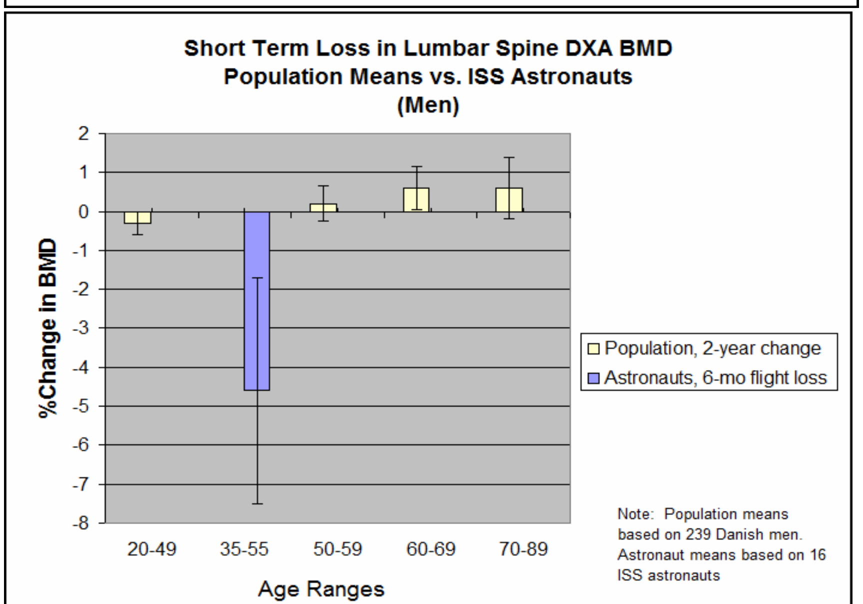
Skeletal Site	Averaged Total Loss (%) at First Postflight Scan
Femoral Neck	**6.7 ± 1.3** n=56
Trochanter	**7.4 ± 1.4** n=55
Pelvis	**7.2 ± 1.7** n=23
Lumbar Spine	**5.0 ± 0.8** n=54
Calcaneus	**2.9 ± 1.0** n=29

International Space Station

BMD Loss vs. Age-matched Loss







Losses in 6 months in space far exceed 2-year losses on Earth in similarly –age population.

Ground-based Research

- **Lower bone volume (with tendancy for thinner trabeculae): <u>suppressed mineralization</u>, decreased BMC with flight.** *Effects of spaceflight on bone mineralization in the rhesus monkey. Zerath E et al. J Appl Physiol 81(1):194, 1996.*

- **<u>Increased biochemical markers for non-mineralized collagen matrix</u> with flight; become normalized upon re-ambulation.** *Nonmineralized and mineralized bone collagen in bone of immobilized monkeys. Mechanic GL et al. Calcif Tissue Int 39(2):63, 1986.*

- **Deep penetration of <u>unrestrained osteoclast activity</u> in cancellous & cortical bone; formation only after 2 months re-ambulation with <u>2-3x MWT</u>.** *Immobilization-associated osteoporosis in primates. Young DR et al. Bone 7(2):109, 1986*.

- **~8.5 months recovery for restoration of normal bending strength in tibial cortical bone. <u>At 15 months BMC not completely restored</u>.** *Tibial changes in experimental diuse osteoporosis in the monkey. Young DR et al. Calcif Tissue Int 35(3):304, 1983.*

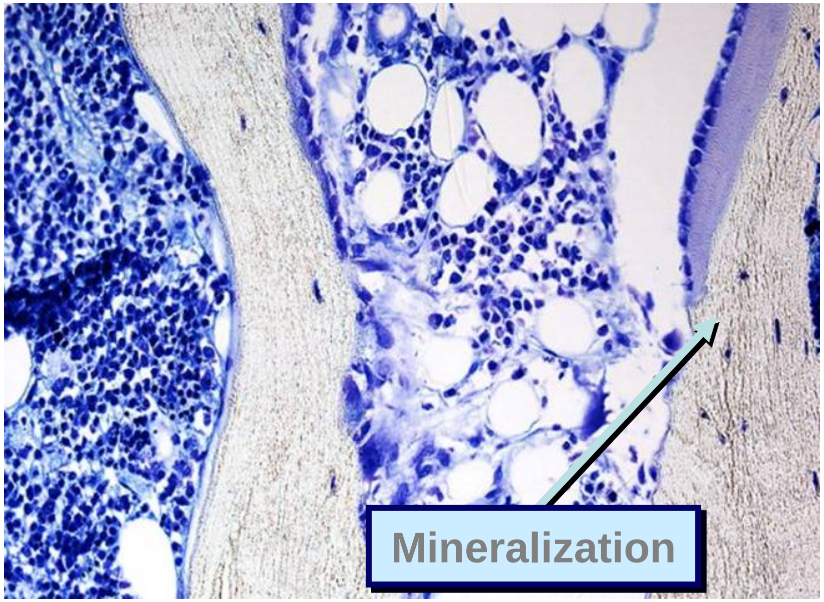
- **Invited Review***: What do we know about the effects of spaceflight on bone? RT Turner. J Appl Physiol 89:840, 2000.*

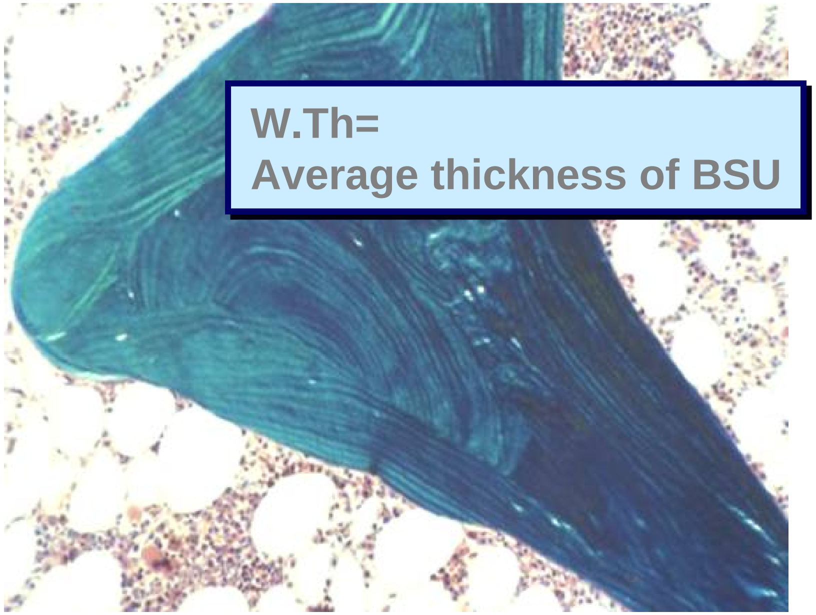
Histomorphometry of Bone Biopsies in Reports of Bed Rest Models

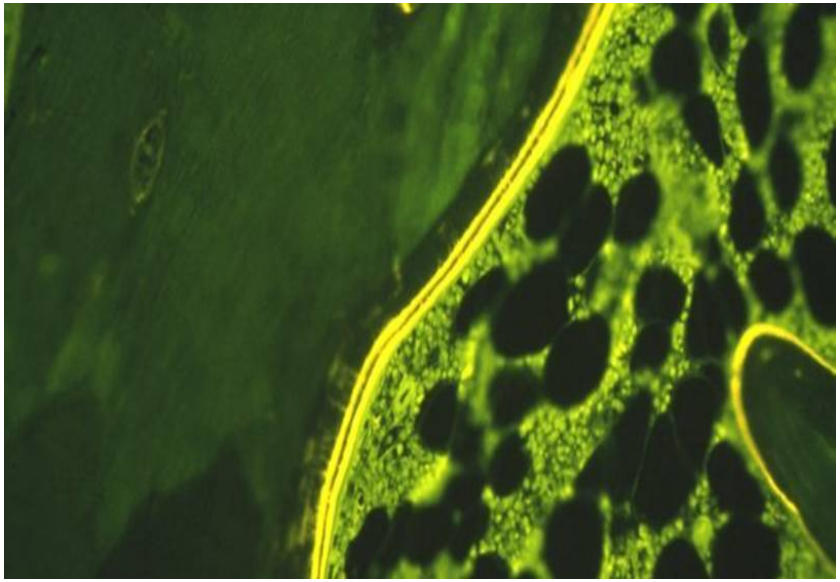
- Vico (1987) a reduced mineralization, no change in matrix formation and increased resorption of bone (osteoclast parameters) with 120 d.
- Arnaud (1992) suppressed bone formation rate and reduced osteoblast activity in as short as 7 d experiment
- Zerwekh (1998) mild decrement in bone-forming osteoblasts concurrent with increased bone resorption in 12 wk study
- Thomsen (2006) deterioration of trabecular microarchitecture 120 d suggestive of aggressive resorption

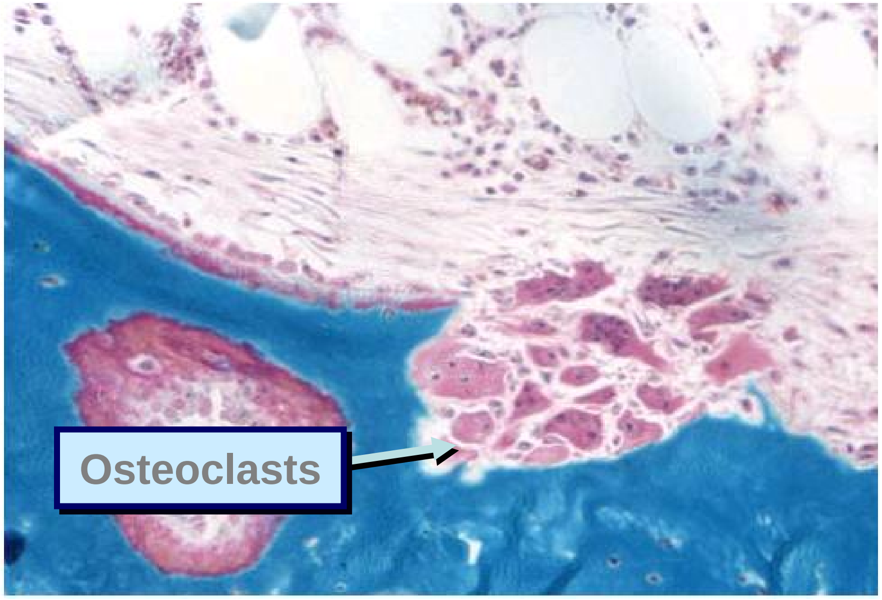
Histomorphometry and biomarker data suggest that bone turnover is <u>unbalanced</u> and that bone coupling is <u>impaired</u> during periods of unloading.

Tissue Measurements

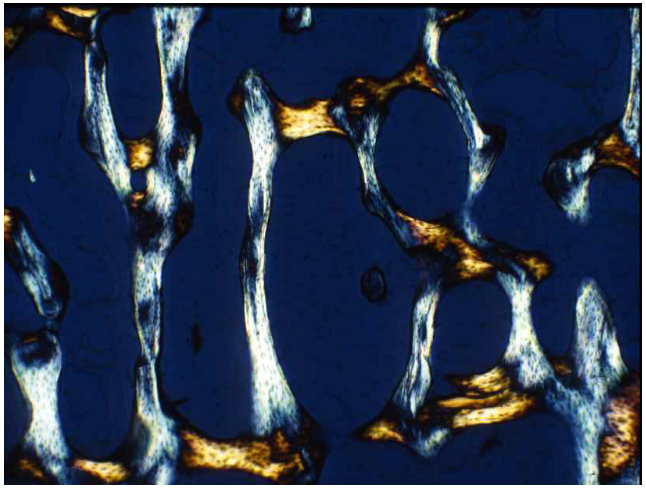


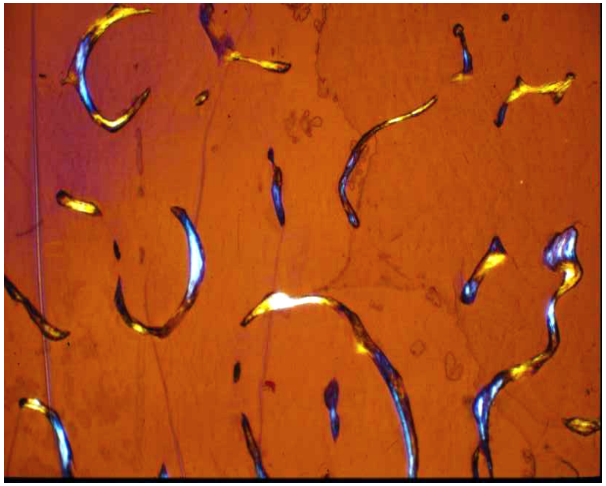


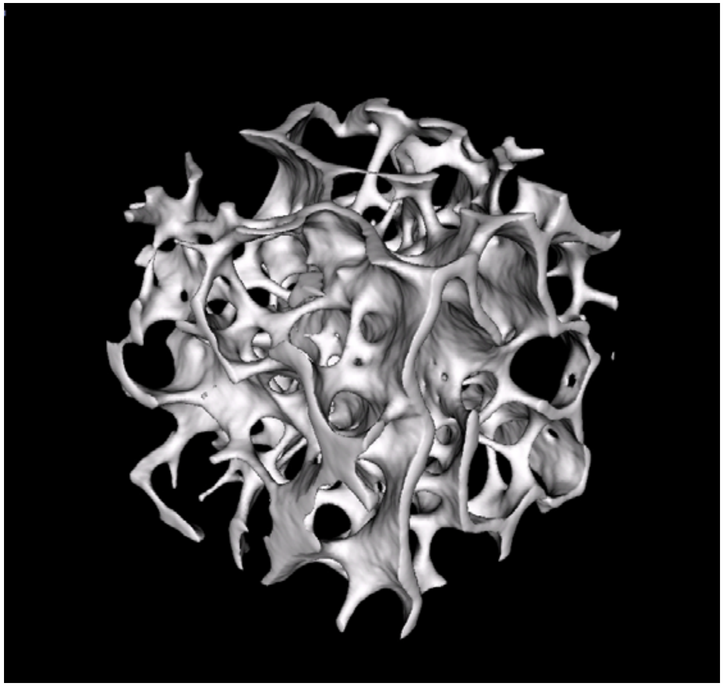


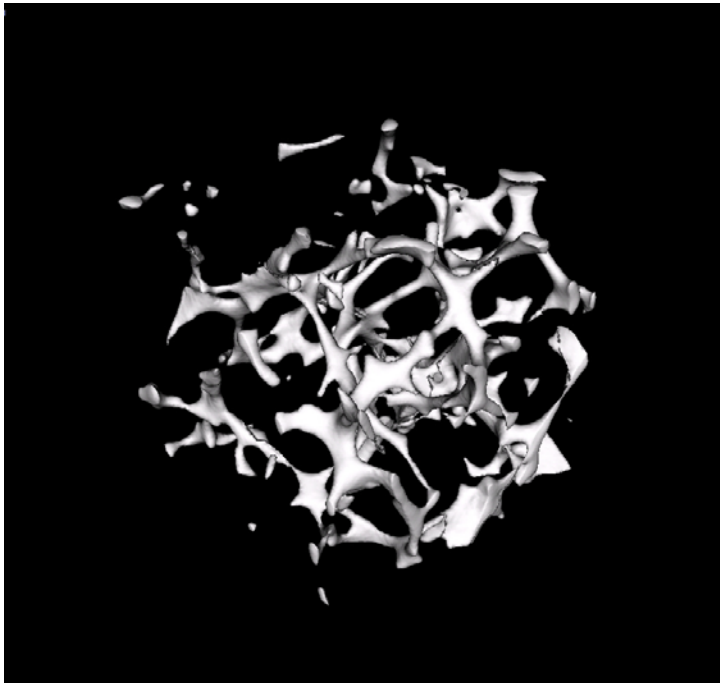


The impact on cancellous bone microarchitecture is unknown.









Summarized Evidence-to-Date

- Increased excretion of calcium, bone degradation products (UNBALANCED BONE RESORTION)
- Reduced absorption of calcium from diet, endocrine changes (IN RESPONSE TO BONE LOSS)
- Accelerated bone resorption (IMPACT ON MICROARCHITECTURE?) and an delayed bone formation/mineralization.
- Site-specific bone atrophy (SIGNALLING NOT SYSTEMIC BUT INITIATED FROM LOCAL SITE – BIOMECHANICALLY-DRIVEN)
- Restoration to preflight status with ambulation or return to Earth. (BMD , bone turnover markers). (WHERE IS BONE MASS BEING REPLACED?)

FYI: Renal Stone Episodes

Astronauts

- 15 total episodes; 3 preflight and 12 postflight (includes Russian cosmonaut)
- Two crew members experience multiple renal stone episodes

Russian Cosmonauts

- 2 cosmonauts identified with urinary calculi
- 1 OF 2 cosmonaut in-flight stone

Pietriczyk, et al. Characteristics of Renal Stone formation among US Astronauts. Aviat Space Env Med. 2007.

RISK FACTORS:
Prevalence of Biochemical Abnormalities in Urine in Astronauts Before and Following Short Duration SF

Abnormality	Preflight	Postflight
Hypercalciuria (>250 mg/day)	20.8%	38.9%
Hypocitraturia (<320 mg/day)	6.9%	14.6%
Hypomagnesuria (<60 mg/day)	6.0%	15.8%
Urinary supersaturation (>2.0)		
Calcium oxalate	25.6 %	46.2 %
Uric Acid	32.8 %	48.6 %
Brushite	19.3 %	13.1 %
Sodium urate	44.9 %	25.8 %

Countermeasures for Bone Loss

- What health risk are we trying to mitigate?

1. Bone fracture
2. Renal Stones
3. Accelerated Osteoporosis

- What endpoints should we use to establish efficacy?

Biological endpoints (reprise)

- **Bone remodeling is <u>unbalanced</u> and <u>uncoupled</u>**
  (BR > BF, mineralization *may* be delayed)

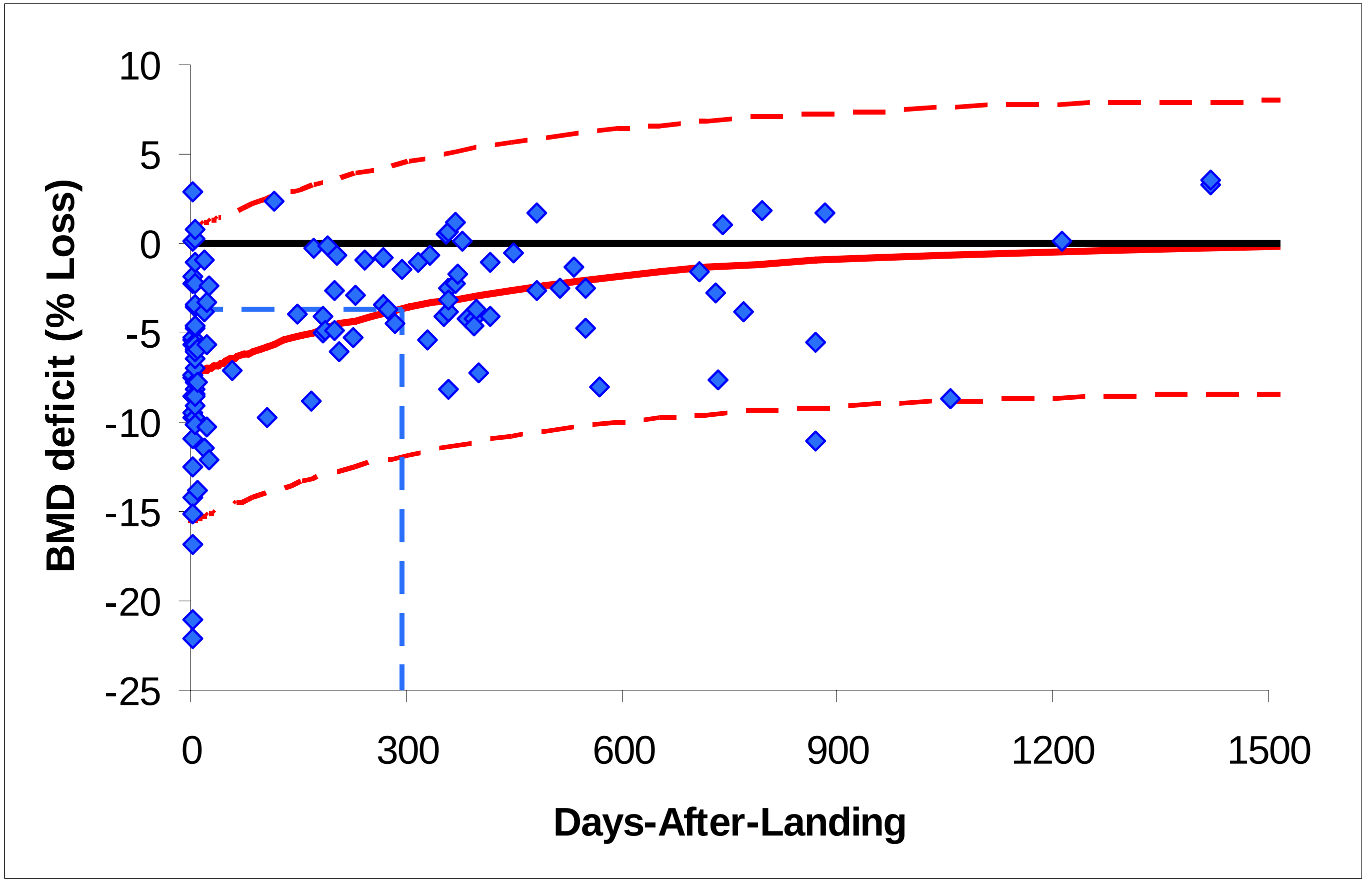
- **Restoration to preflight status with ambulation or return to Earth. (BMD , bone turnover markers)**
  (BR markers reduced, BF markers stimulated, BMD restored at period greater than time in space)

- **Restoration of BMD (by DXA) not necessarily restoration of bone strength.**

- **Demineralization of bone can decrease strength and increase risk for renal stone formation**
  (Factor of Risk depends on Applied forces to Bone strength; urine saturation documented postflight)

Recovery of BMD with return to gravity: what about bone strength?

$L_t = L_0 * \exp^{\ln(0.5)*t/HL}$

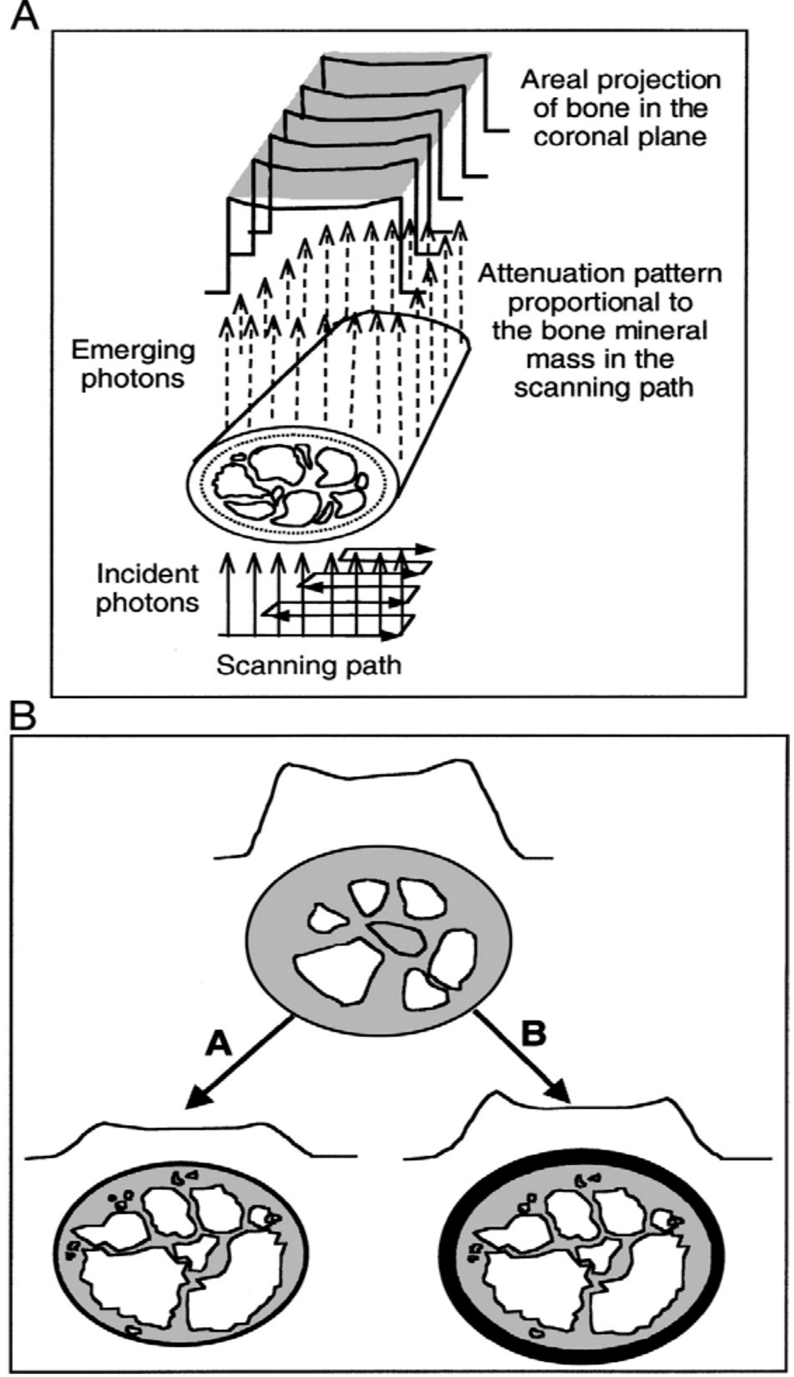


Trochanter BMD of ISS & Mir Crewmembers
Loss0=7.4% Recovery Half-life=276 d

Use of Imaging Technology to evaluate changes in bone mass

Adding Bone Mass does not necessarily replace lost bone.

Does it matter?



DXA Measurement

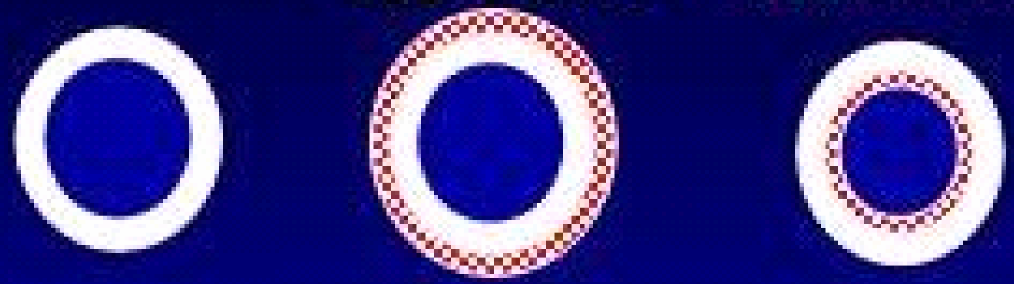
Skeletal Response

Seeman, E. J Clin Endocrinol Metab 2001;86:4576-4584

The Journal of Clinical Endocrinology & Metabolism

Mary Bouxsein, Ph.D.

Physiological Changes in Bone Geometry



	Baseline	Periosteal Apposition	Endosteal Apposition
Periosteal Diameter	100 %	110 %	100 %
Endosteal Diameter	100 %	100 %	90 %
Compressive Strength	100 %	148 %	125 %
Bending Strength	100 %	168 %	116 %

With multiple facets of skeletal decline, how do you select a countermeasure?

Current and proposed flight countermeasures

Exercise Countermeasure

A substitute for terrestrial loading that will maintain or minimize bone loss due to disuse.

History of Space Exercise

GEMINI
- Isometrics
- Bungee exercise

APOLLO
- Rope-pull system

SKYLAB II
- Cycle ergometer

SKYLAB III
- Cycle ergometer
- MKI isokinetic rope-pull
- MKII handle/spring assembly

SKYLAB IV
- Cycle ergometer
- MKI isokinetic rope-pull
- MKII handle/spring assembly
- Treadmill

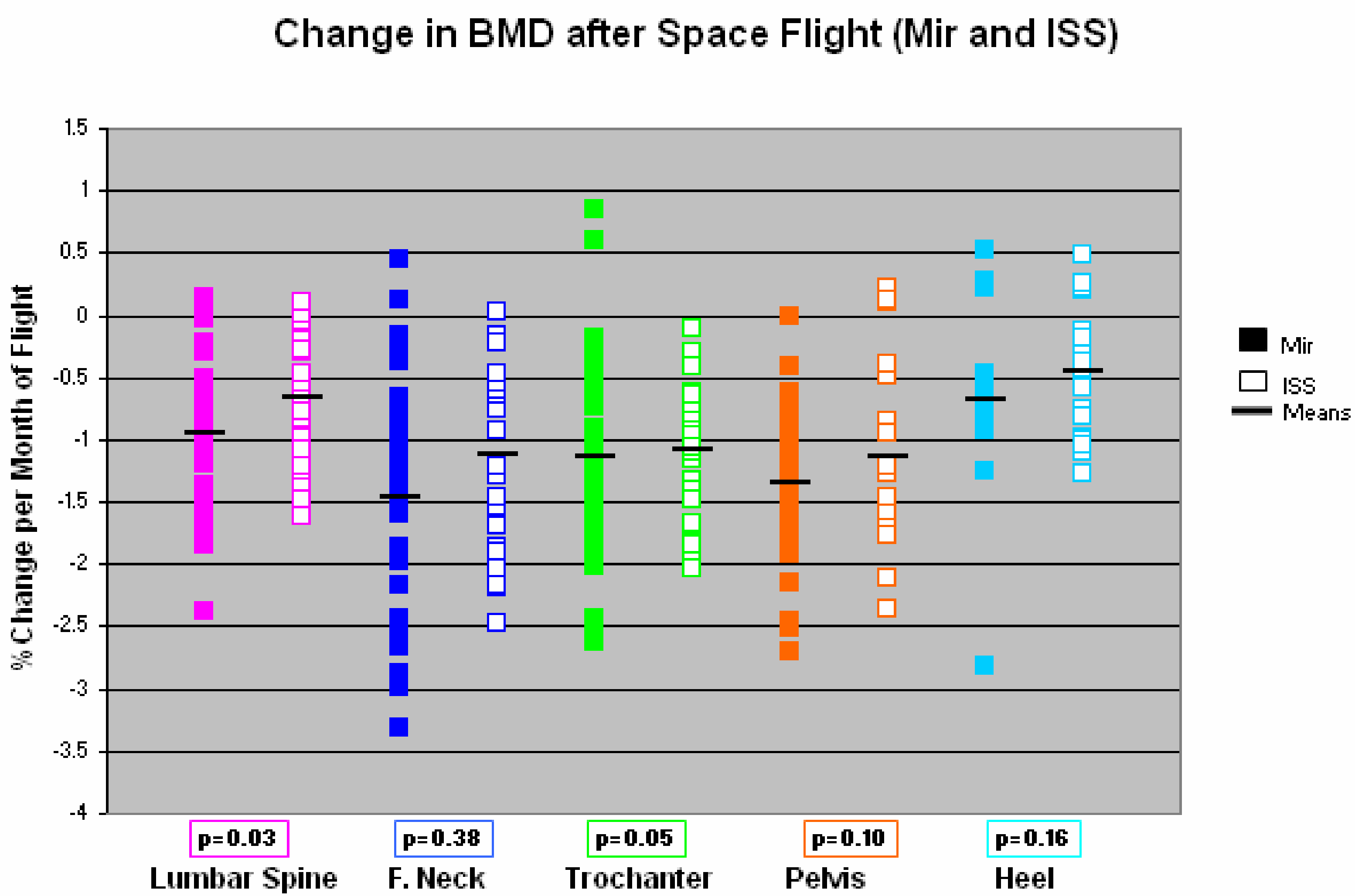
SHUTTLE
- Cycle ergometer
- Rower
- Treadmill

SOYUZ-SALYUT & MIR
- Cycle ergometer
- Treadmill
- Penguin Suit
- Russian Expanders

International Space Station
- Cycle Ergometer (CEVIS)
- Velo Ergometer
- Treadmill (TVIS)
- Penguin Suit
- Resistance Exercise Device (iRED)
- Russian Expanders

Slide courtesy of
Judith Hayes
Exercise Summit
October 2003

Flight Exercise as a Countermeasure



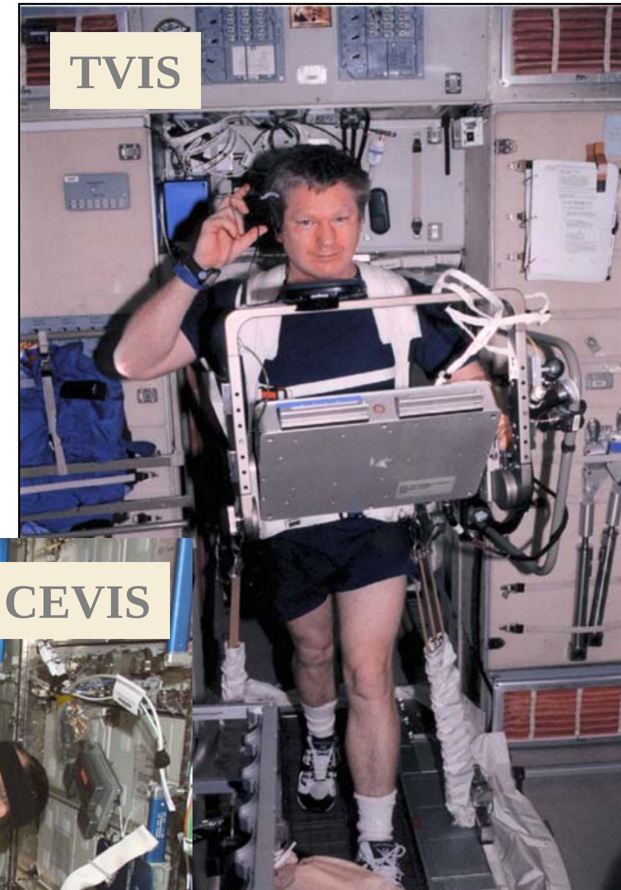
p values based on one-tailed t-test assuming equal variances, ISS vs. Mir

For spine and hip, n = 16 ISS astronauts, 9 ISS cosmonauts, 7 Mir astronauts and 29 Mir cosmonauts (7 repeat flyers)

For pelvis, n = 16 ISS astronauts, 0 ISS cosmonauts, 7 Mir astronauts and 19 Mir cosmonauts

For heel, n = 16 ISS astronauts, 9 ISS cosmonauts, 7 Mir astronauts and 0 Mir cosmonauts

ISS Exercise Devices (U.S.)



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ISS Exercise Countermeasure: Ineffective?

- Limitations in hardware under weightless conditions and operational constraints
- Operation failure
- Data acquisition failure
- No baseline data
- No standardized exercise prescription
- Crew preference
- Will <u>exercise</u> mitigate skeletal response to weightlessness?

Countermeasures developed for Flight must first be tested in a flight analog.

Disuse osteoporosis induced by prolonged bed rest.

JSC Flight Analog Bed Rest Project at UTMB

- Created in response to need for bed rest studies due to limited in-flight resources.
- Overall objective - the development and evaluation of countermeasures prior to validation in a flight scenario.
- Cooperation with International Partners
- Conditions standardized
- Collection of Standard Measures for every bed rest subject.
- Integrated campaigns of individual bed rest investigations from external scientists

JSC Flight Analog/Bed Rest Project: Standard Conditions

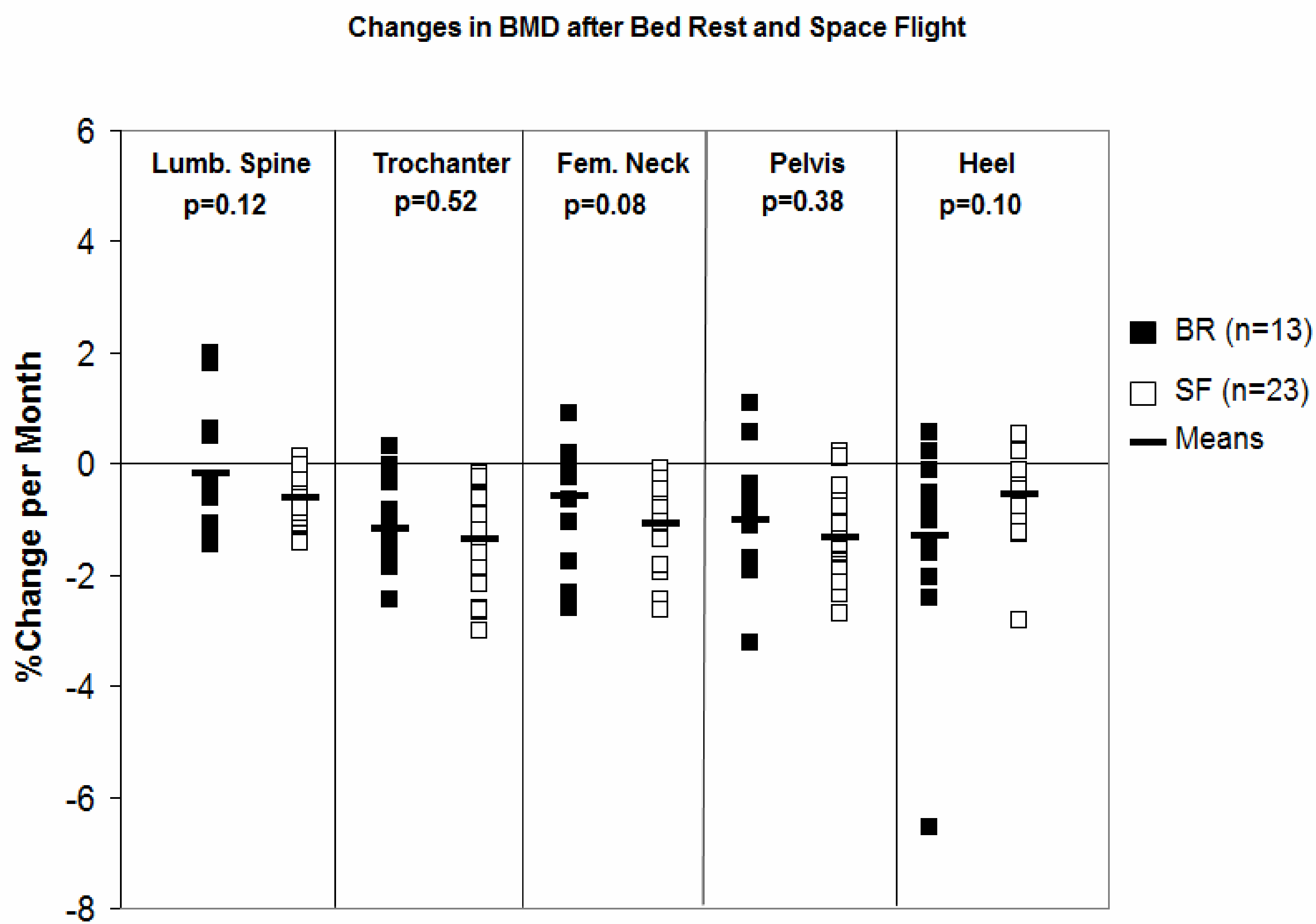
- **Environmental: 68-76^{0} F and 40-60% RH**
- **Bed Position: 6 degrees head down tilt, continuous for the duration of the study**
- **Duration: 60-90 days**
- **Wake 0600, light out 2200 hrs (strictly enforced, no napping)**
- **Daily vitals:**
  - **blood pressure**
  - **heart rate**
  - **body temperature**
  - **respiratory rate**
  - **body weight (bed scale)**
- **Intake and output measurements**
- **Standardized diet, all consumed**

Flight Analog vs. Spaceflight Effect Regional Changes in BMD

Table I. Regional changes in BMD with various durations of bed rest.

Bed Rest Duration:	47 days (n=4)	60 days (n=9)*	90 days (n=6)
	% Change Avg ± SD	% Change Avg ± SD	% Change Avg ± SD
Lumbar Spine	-0.1 ± 2.3	-1.5 ± 1.8 †	+0.6 ± 3.2
Trochanter	-1.5 ± 1.1 †	-2.7 ± 2.0 ‡	-4.1 ± 2.2 ‡
Femoral Neck	-0.4 ± 0.9	-1.8 ± 2.4 †	-1.2 ± 2.2
Total Hip	-1.5 ± 0.6 †	-2.6 ± 1.7 ‡	-3.5 ± 1.3 ‡
Pelvis	+0.3 ± 1.2	-4.7 ± 3.0 ‡	-4.9 ± 2.7 ‡
Heel	-1.7 ± 1.1 †	-2.5 ± 5.0	-4.5 ± 8.0
Distal Radius	+1.2 ± 3.7	-0.2 ± 1.7	-1.5 ± 0.9 ‡

*The 9 subjects include the 6 Study 2 and Study 4 (90d) subjects measured at the 60-day time point. †p<0.05 ; ‡p<0.01



SF subjects are 23 U.S. Astronauts from Mir and ISS flights; BR subjects are 13 Controls from JSC Bed Rest studies.

Exercise Countermeasures in Bed Rest Studies

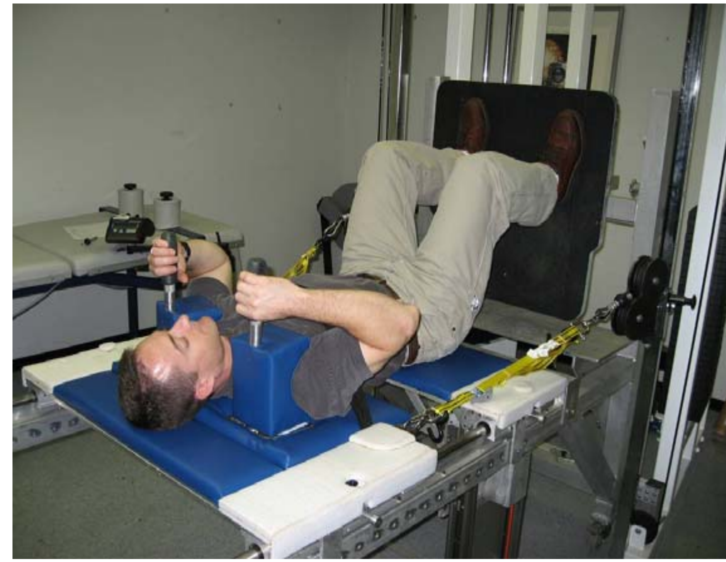
- Watanabe Y, et al. *Intravenous pamidronate prevents femoral bone loss and renal stone formation during 90-day bed rest. J Bone Miner Res 19(11):1771, 2004.*
- *Smith SM, et al. Evaluation of treadmill exercise in a lower body negative pressure chamber as a countermeasure for weightless-induced bone loss: a bed rest study with identical twins. J bone Miner Res. 18(12):223, 2003.*
- Shackelford L, et al. *Resistance exercise as a countermeasure to disuse-induced bone loss. J Appl Physiol. 97:119, 2004.*
- Rittweger J, et al. *Muscle atrophy and bone loss after 90 days' bed rest and the effects of flywheel resistive exercise and pamidronate: Results from the LTBR study. Bone. 35(6):1019, 2005.*

Exercise appears to <u>attenuate</u> bone loss (higher BMD compared to non-exercising controls) but does not prevent resorption.

Is it attenuation or adding bone mass to another site?

Look to Cavanagh reports; reports on LBNP

Unloaded Exercise Performance



Measures of Skeletal Response to Analog and Exercise Countermeasure

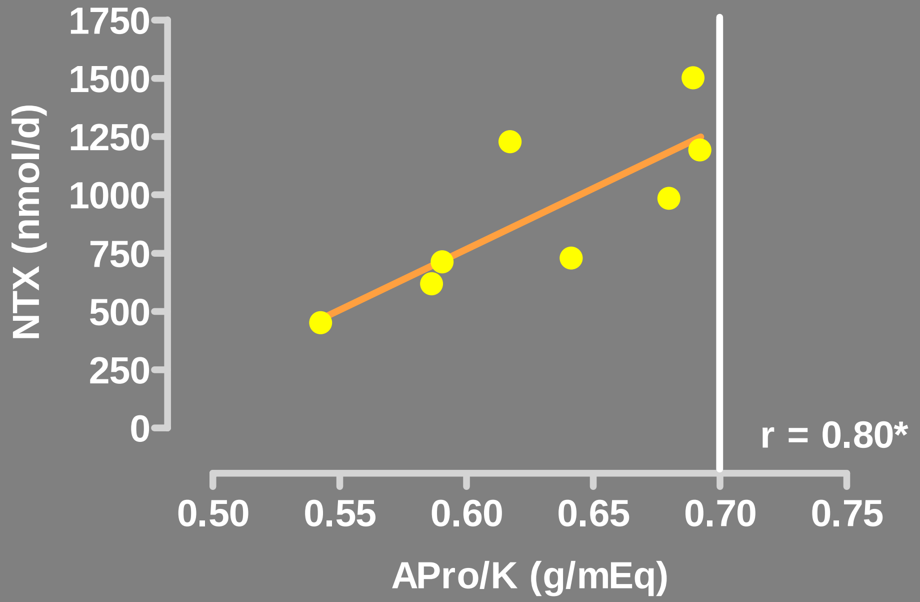
- Ground Reaction Forces
- QCT of hip and attached muscles
- Proposed Microarchitecture of distal tibia
- Proposed (RANK-L and OPG levels)
- DXA BMD
- pQCT (recently added standard measure)
- Bone biomarkers

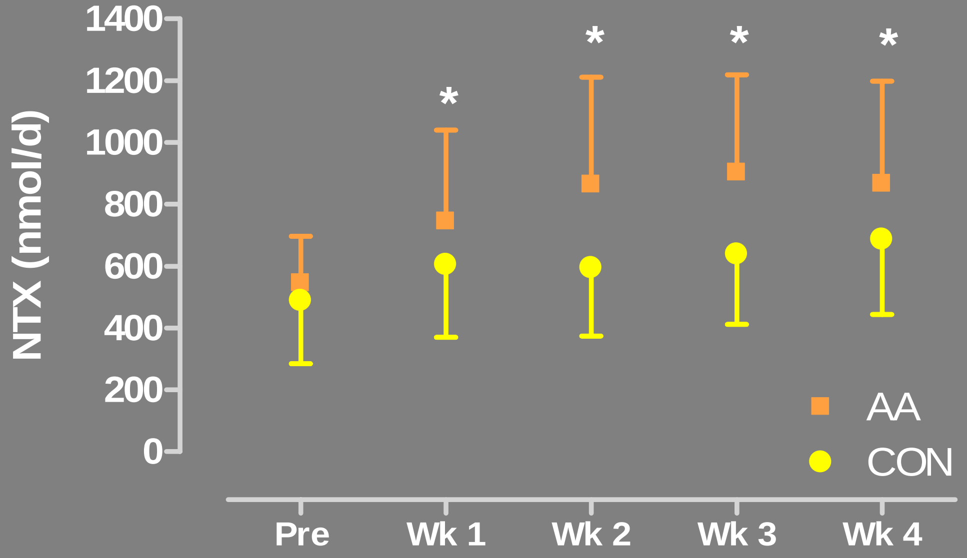
DIFFICULT TO TRANSLATE EXERCISE LOADS TO ACTUAL LOADS EXPERIENCED BY BONE IN HUMAN STUDIES.

Nutrition Countermeasure

Slide courtesy of
Scott M. Smith, Ph.D.

Protein/Bone

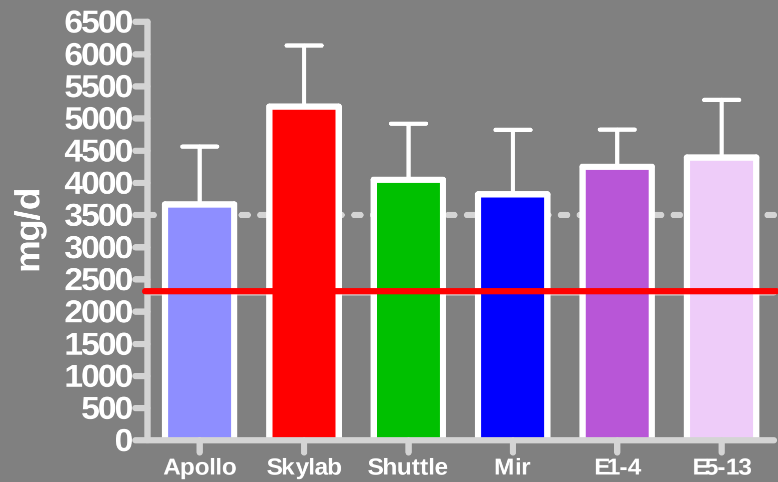


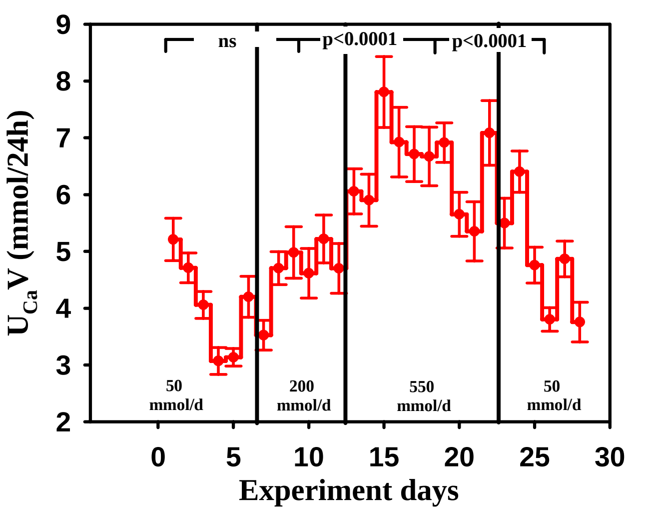


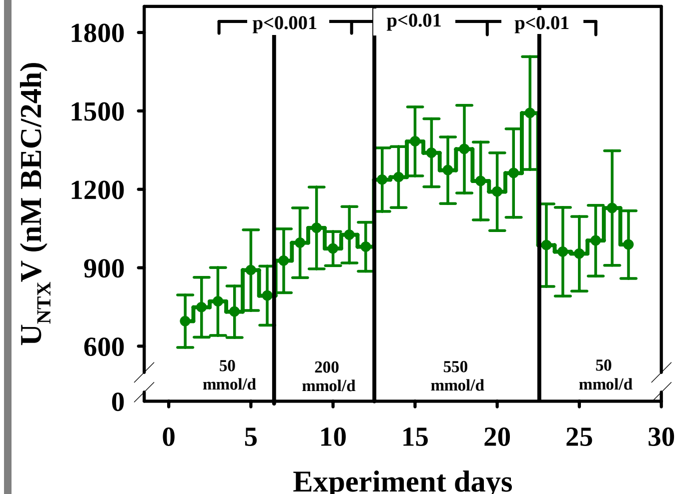
Zwart et al., *AJCN*, 2004
Zwart et al., J Appl Physiol, 2005

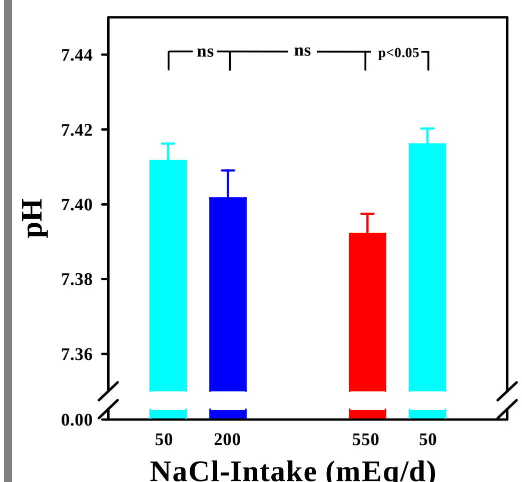
Slide courtesy of
Scott M. Smith, Ph.D.

Sodium









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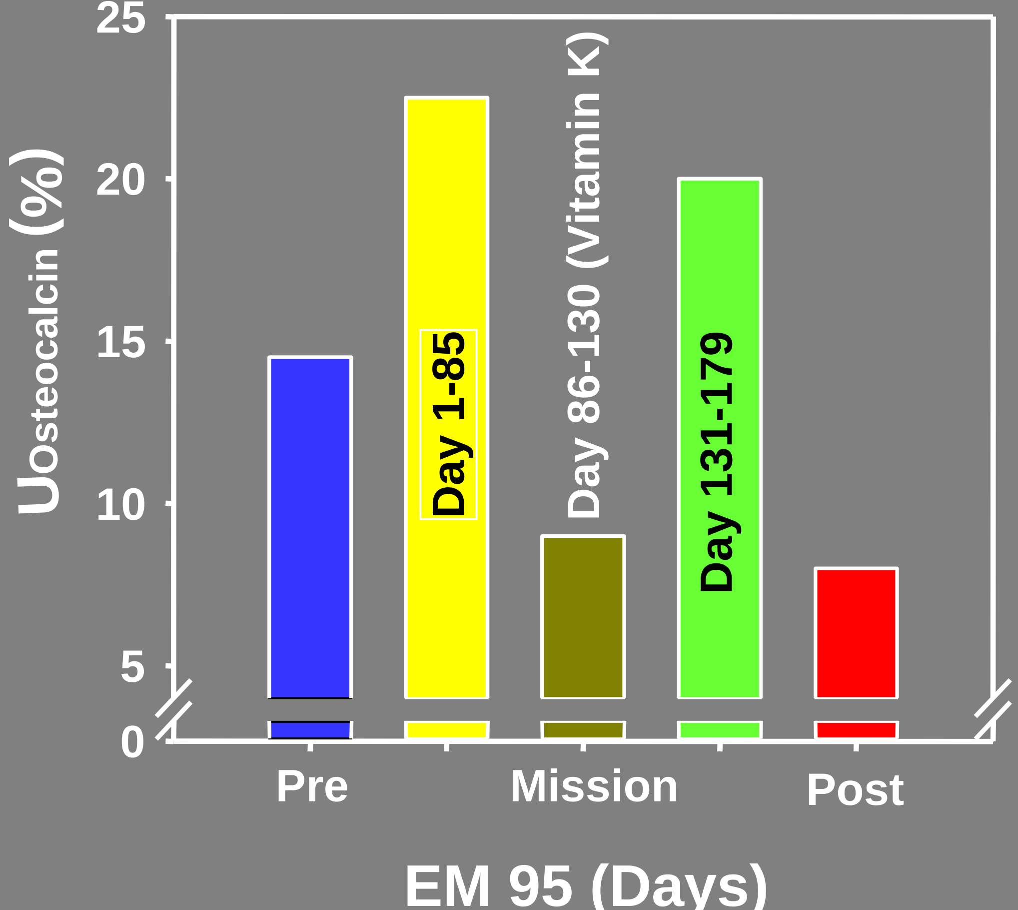
Vitamin K

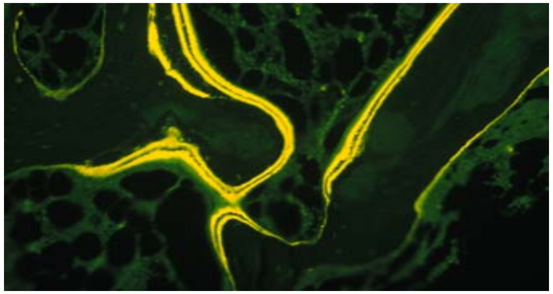


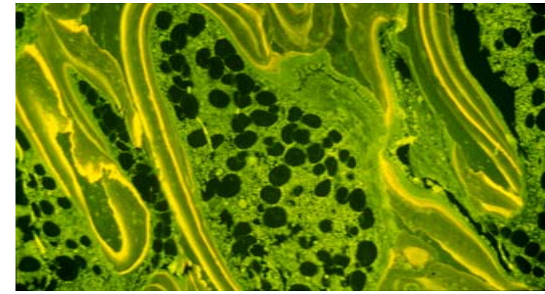
The role of diet in bone health may go well beyond calcium and vitamin D

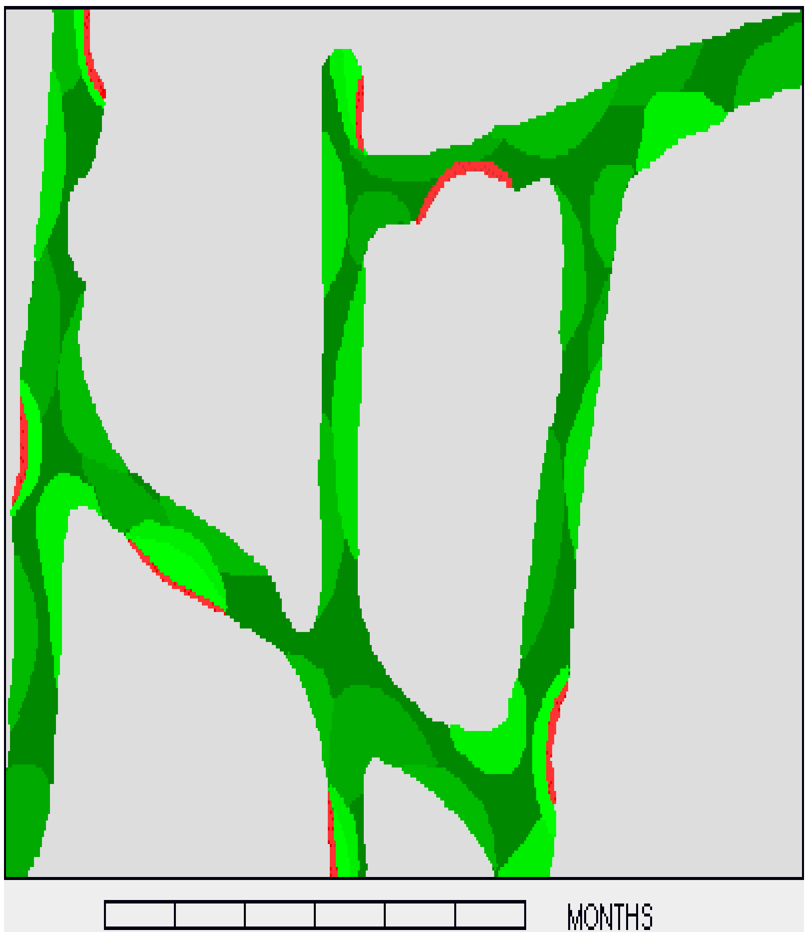
Caillot-Augusseau et al., Clin Chem 2000

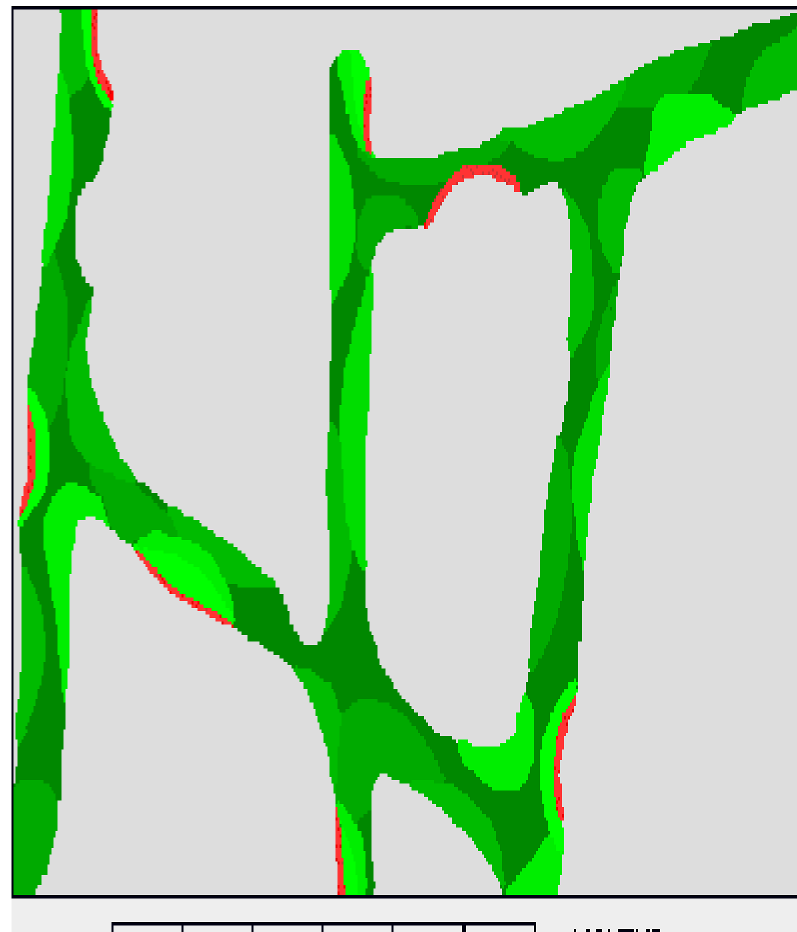
Pharmaceutical Countermeasures

Normal vs. High Bone Turnover







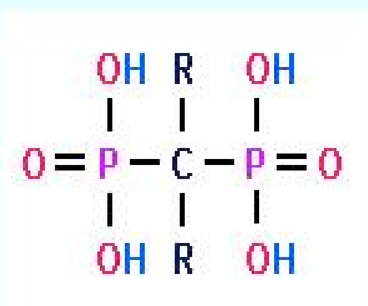


Class of Antiresorptive Agents

http://courses.washington.edu/bonephys/ophome.html

Bisphosphonates

etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva)

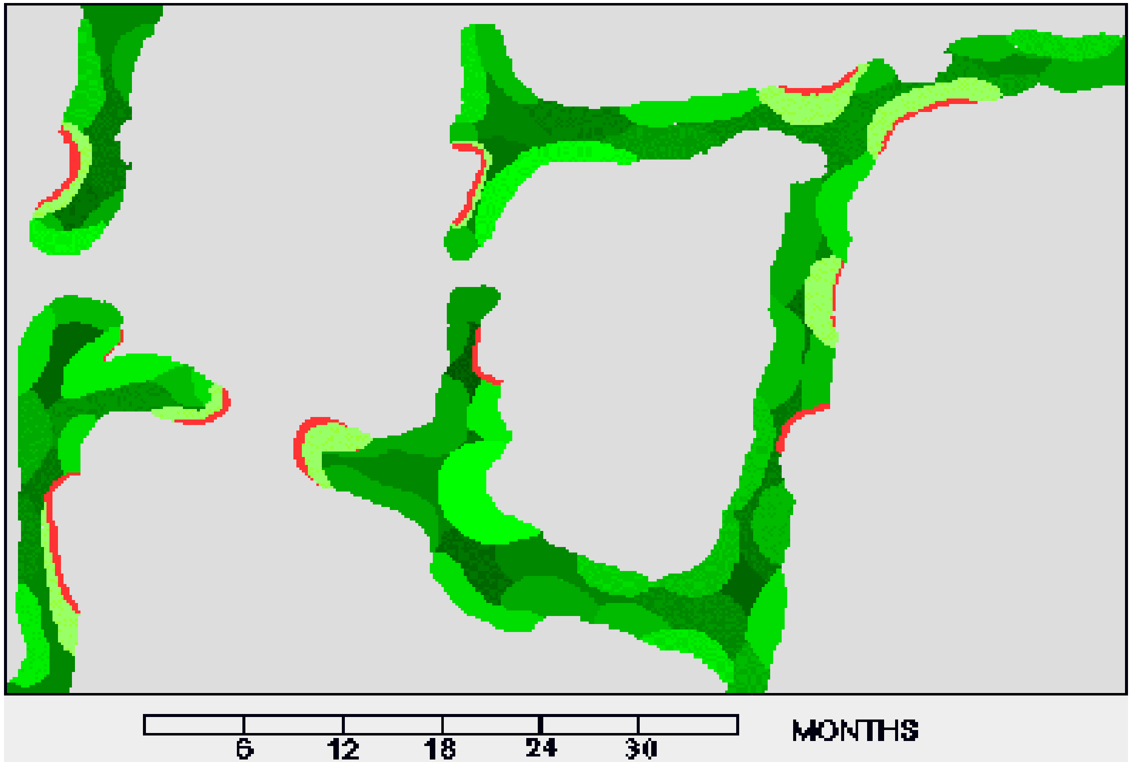


- Indications
- Side effects
- Dose
- Short term evidence
- Use in elderly patients
- Long term effects
- Etidronate and other bisphosphonates in osteoporosis
- Effects of bisphosphonates on bone
- Effects during pregnancy
- Jaw osteonecrosis
- References

Bisphosphonates

PHYSIOLOGIC EFFECTS
* Decreased bone resorption
* Decreased bone formation by 70-95%
* Increased mineralization density
* Slight increase in bone volume
* Increase bone strength first 5 years
* Decreased fracture rate first 5 years, compared to placebo
* Half-life in bone greater than 10 years
* Increased micro-damage in animals
* Long-term effects on bone unknown

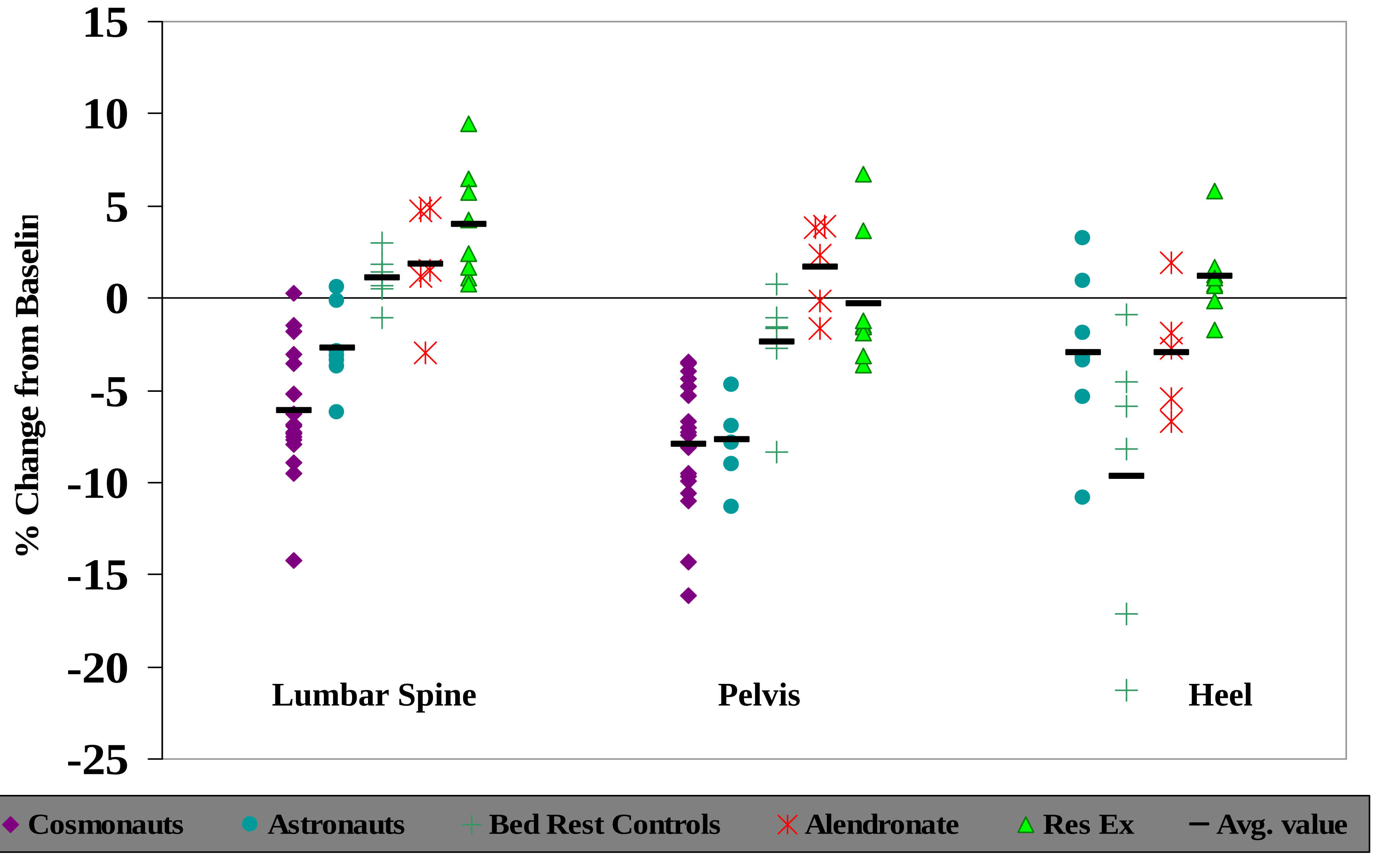
Bisphosphonate Effect on Remodeling



Slide courtesy of JSC Bone and Mineral Lab

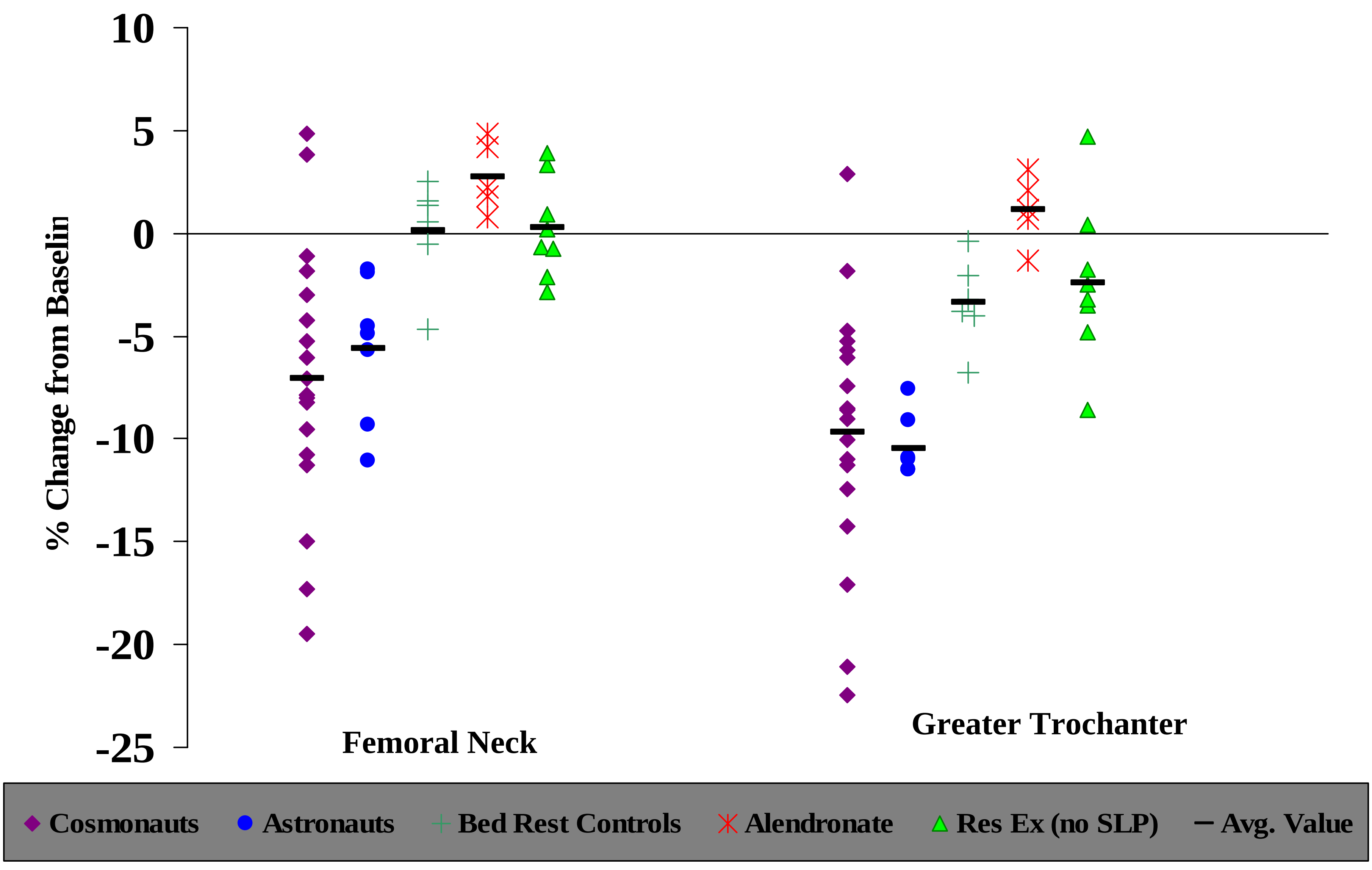
Percent Changes in Regional BMD

Space Flight and Bed Rest

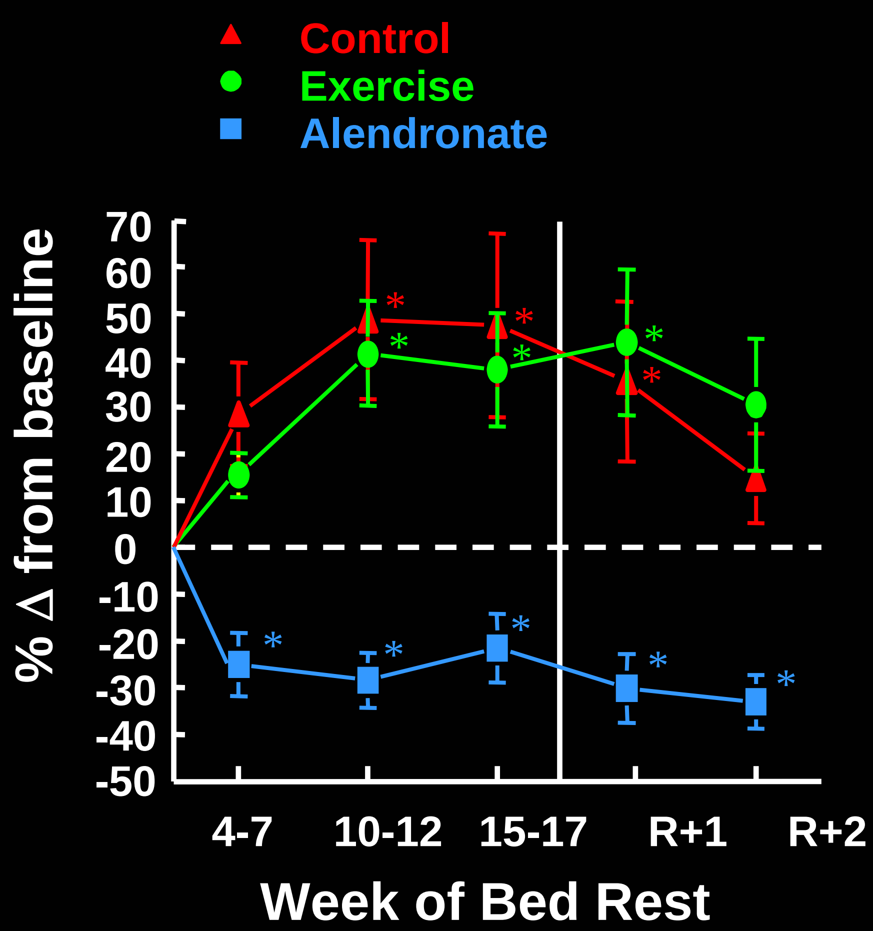


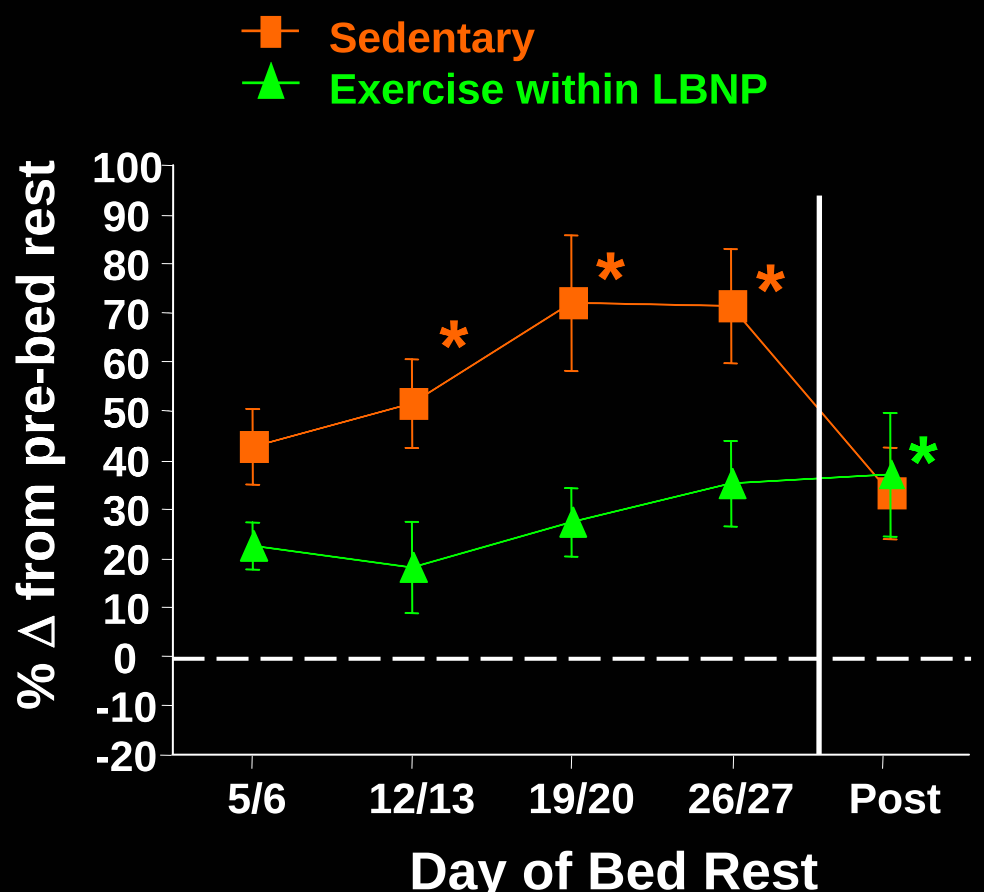
Percent Changes in Regional BMD

Space Flight and Bed Rest



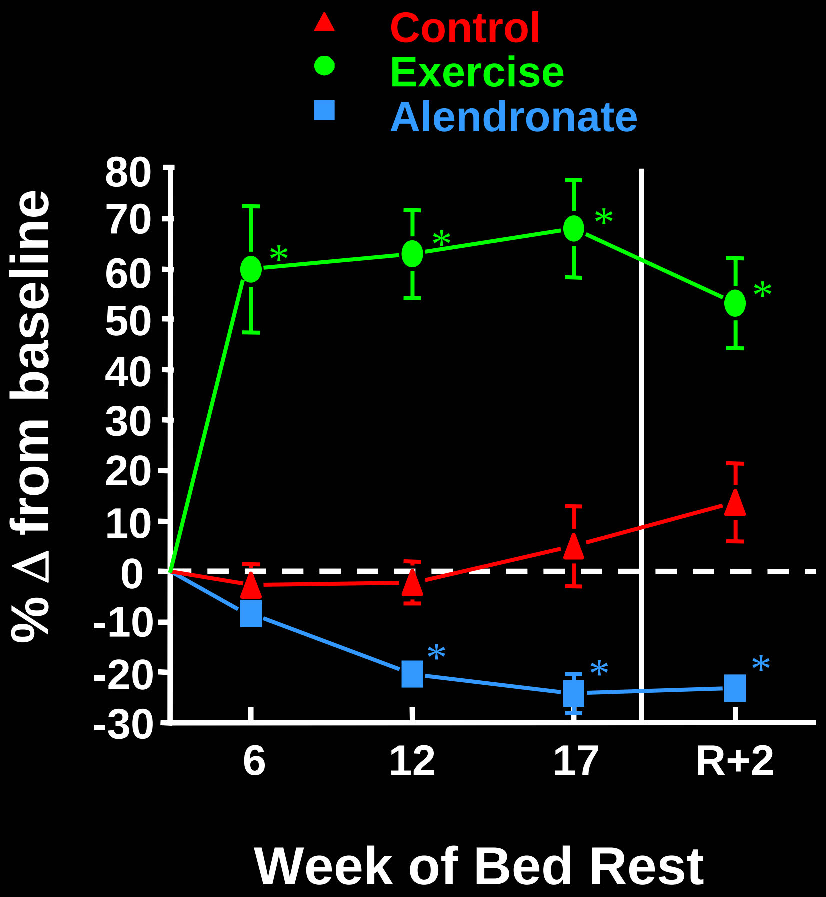
Bone Resorption

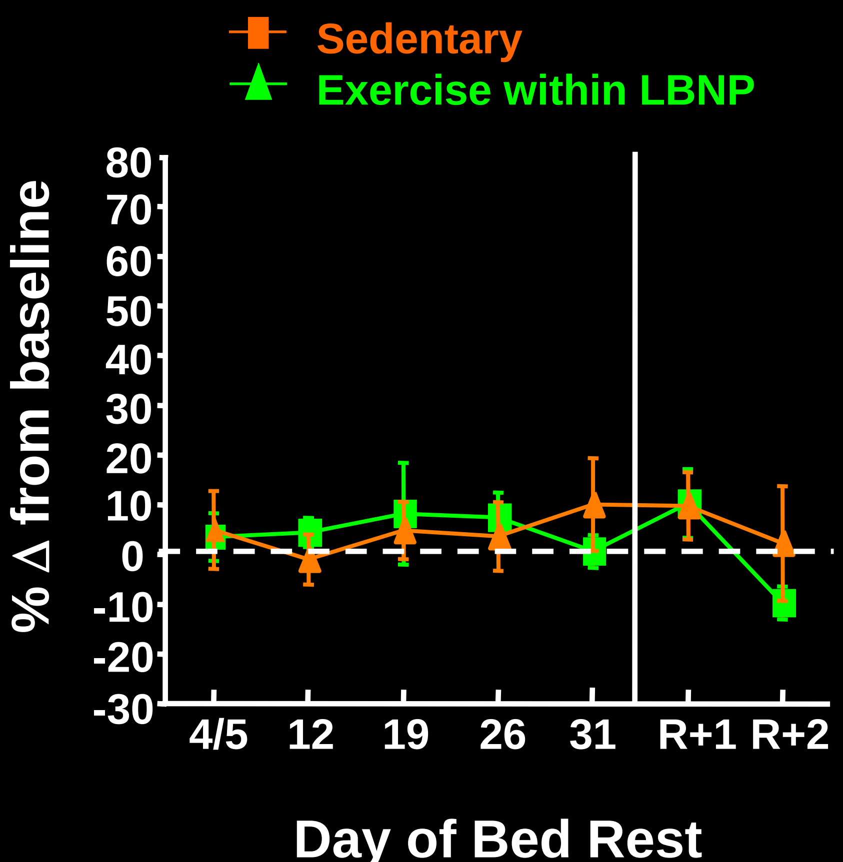




Smith et al., 2003
Le Blanc et al., 2002
Shackelford et al., 2004

Bone Formation





Smith et al., 2003
Le Blanc et al., 2002
Shackelford et al., 2004

Developing Exercise as an Effective Countermeasure

Exercise as a Countermeasure

- Multiphysiological impact
- Psychological, musculoskeletal, metabolic
- Motivated crew members
- No drug side effects

- No standardized Px
- Time constraint, up-mass
- Is impact loading essential and can it be produced?
- How can exercise a countermeasure be evaluated in the JSC flight analog?

Factor of Risk = *Applied Load / Fracture Load

"Factor of Risk" for Fracture

» "Exercise" can decrease numerator AND increase denominator

» Numerator: improve neuromuscular coordination of lower extremities thereby reducing energy of fall ("breaking the fall" changing orientation)

» Numerator: prevent loss in mass of postural muscles (preserve balance and reduce falls)

» Denominator: increase BMD (reducing fragility)

A Countermeasure for fracture risk should reduce applied loads or improve fracture load of bone. Anti-resorptives? Engineering? Selection criteria?

Five principles for designing an effective exercise countermeasure

(C Snow and B Beck)

- **<u>Specificity-</u>** *protocol that targets specific bone sites (muscle area)*
- **<u>Overload</u>** – *stimulation comes from overloading the bone*
- **<u>Reversibility</u>** *–reversal in bone response after stimulus is removed (physically fit adults)*
- **<u>Initial values</u>** – *greatest response from bone when beginning levels are lower than average (selection)*
- **<u>Diminishing Returns</u>** – *once training level is achieved, response is slow and small (understudied)*

Limitations of Exercise Countermeasure

- Preferential loading of dominant limb increases cortical but not cancellous (aka trabecular) bone. (Adami S et al J Bone Miner Res 1999; 14:120-124.)
- Lang (2005) and Vico (2000) report greater % loss in cancellous bone.
- High fracture risk sites (hip, lumbar spine) have greater amount cancellous bone.

Limitations of Exercise Countermeasure.2

- Limited information on the cellular and tissue response of bone to exercise – changes to remodeling process (animals)

- Exercise approach to <u>prevent</u> bone loss in adult skeleton (through indirect effects on catabolism-resorption) and not as a restorative countermeasure (anabolic effect).

Local mechanical forces created by physical activity regulate osteoblast and osteoclast activity

- Mechanical cues regulate skeletal development and adaptation to different physical activities and environments-----Throughout life

- Magnitude of Loads more important than cycles.

Exercise Bone Physiologist

- **Exercise has the potential to change bone strength by changing bone geometry.**

- **Exercise can maintain or build bone in adult skeleton when *Loads of >2.5x BW at hip and spine*.**

B. Beck and C. Snow

(Exercise in the prevention of osteoporosis-related fractures. In: Osteoporosis: pathology and clinical management. Humana Press, Totowa, NJ)

Exercise Countermeasures in Bed Rest Studies (reprise)

- Watanabe Y, et al. *Intravenous pamidronate prevents femoral bone loss and renal stone formation during 90-day bed rest. J Bone Miner Res 19(11):1771, 2004.*
- *Smith SM, et al. Evaluation of treadmill exercise in a lower body negative pressure chamber as a countermeasure for weightless-induced bone loss: a bed rest study with identical twins. J bone Miner Res. 18(12):223, 2003.*
- Shackelford L, et al. *Resistance exercise as a countermeasure to disuse-induced bone loss. J Appl Physiol. 97:119, 2004.*
- Rittweger J, et al. *Muscle atrophy and bone loss after 90 days' bed rest and the effects of flywheel resistive exercise and pamidronate: Results from the LTBR study. Bone. 35(6):1019, 2005.*

Exercise appears to <u>attenuate</u> bone loss (higher BMD compared to non-exercising controls) but does not prevent resorption.

Since building bone in space will require large stresses (magnitude of load), perhaps the best use of **exercise in** the adult skeleton is for preserving bone mass through the indirect effect on attached muscles.

That is, prevent bone atrophy by preventing muscle atrophy and maintaining forces on bone to which muscles are attached.

Efficacy in Countermeasure for Bone Loss

- Ability to suppress excretion of bone mineral (calcium, or indirect measure of BR biomarkers). *Addresses 2 risks*
- Ability to mitigate site-specific losses of BMD in hip and spine. (changes bone mass)

<u>Supplement</u> CM with

- "engineering," e.g. to reduce applied forces,
- osteoprotective suit designs,
- good nutrition and hydration,
- reduce risk for falling (neuromuscular control)
- optimal crew selection

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